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Maternal nutrition and gastrointestinal atresia/stenosis:
National Birth Defects Prevention Study 1997-2009

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2013

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An abstract of
a thesis submitted to the Faculty of the
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Abstract

Maternal nutrition and gastrointestinal atresia/stenosis:

National Birth Defects Prevention Study 1997-2009

By Marcy L. Schaeffer

This thesis investigates the association between maternal nutrition (as measured by dietary intake of macronutrients, micronutrients and vitamins, and elements) in the year before pregnancy and risk for gastrointestinal atresia/stenosis (esophageal, duodenal, jejunal/ileal, and anorectal). Due to the increasing prevalence of obesity among reproductive-age women, maternal nutrition before and during pregnancy is of growing interest in the study of birth defects, but the association between specific nutrients and gastrointestinal atresia/stenosis is not well-understood. The associations between maternal nutrition and these gastrointestinal atresia/stenosis were examined using data from the National Birth Defects Prevention Study (NBDPS) and pregnancies with estimated dates of delivery between 1997 and 2009. The categories of gastrointestinal atresia/stenosis included in the analysis were identified based on case definition criteria developed by clinical geneticists at each Center. Controls were liveborn infants with no major birth defects randomly selected based on the proportion of number of births in the same geographic area from which the cases were ascertained. Covariate and nutritional information was obtained from a computer-assisted telephone interview (CATI) with case and control mothers. We chose to focus on the maternal characteristics of maternal age, race/ethnicity, education, pre-pregnancy body mass index (BMI), first trimester nausea/vomiting, and use of folic acid supplements and Study Center as covariates for our analyses. We examined the differences in these covariates between case and control mothers with chi-square tests of association and crude odds ratios. We computed multivariate logistic regression models for each gastrointestinal atresia/stenosis and obtained adjusted odds ratios of risk of each gastrointestinal atresia/stenosis by quartile of nutrient intake, adjusting for all covariates and average total energy intake. Our crude analyses showed that the maternal characteristics associated with esophageal and anorectal atresia/stenosis risk were generally consistent with previous studies. Our adjusted odds ratios did not support clear associations between the examined macronutrients, micronutrients/vitamins, and elements, and risk for esophageal, duodenal, jejunal/ileal, or anorectal atresia/stenosis. Some visual trends between risk for the gastrointestinal atresia/stenosis outcomes and quartiles of nutrient intake suggest that further investigation might be warranted.

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CHAPTER I

Introduction/Background

One in thirty-three infants in the United States are born with a birth defect [1]. However, the cause of most birth defects are unknown [2]. Surveillance systems and research programs have been developed in the United States over the past several decades to identify and classify these defects, monitor their occurrence, and investigate their risk factors through epidemiologic and genetics research.

Due to the increasing prevalence of obesity among reproductive-age women, maternal nutrition before and during pregnancy is of growing interest in the study of birth defects [3-5] (Figure 1). Data from previous studies indicate that nutritional status before and during early pregnancy is related to pregnancy outcomes [6]. Periconceptional folic acid consumption, for instance, has been well-documented to reduce risk for neural tube defects (NTDs) [7-10]. In addition, periconceptional multivitamin use has been observed in multiple studies to reduce risk for birth defects other than NTDs [11]. The association between specific nutrients and many specific birth defects, including gastrointestinal atresia/stenosis, however, is not well-understood.

The largest population-based birth defects case-control study in the United States is the National Birth Defects Prevention Study (NBDPS). NBDPS is a multi-center study funded by the Centers for Disease Control and Prevention. NBDPS collects information from mothers of both case and control infants in hopes of connecting pregnancy exposures, including nutritional status, with specific birth defects. Esophageal, duodenal, jejunal/ileal and anorectal atresia/stenosis are among the specific defect categories included in NBDPS, and will be examined in this thesis.

Esophageal atresia/stenosis is a condition in which there is an absence of a normal opening in the esophagus (atresia) or a narrowing or constriction of the diameter of the esophagus (stenosis), is estimated to occur in 2.17 per 10,000 live births [12]. Esophageal atresia/stenosis is the most common esophageal congenital malformation, yet its etiology is not well-understood [13]. The esophagus and trachea emerge from a common tube in the developing fetus and divide into two separate organs during the fourth to the eight week of gestation. During this division, a failure of the primitive foregut to recanalize, usually causing the upper esophagus to end and not connect to the lower esophagus and the stomach, leads to esophageal atresia. Esophageal atresia occurs as an isolated anomaly in 7% of cases, while 93% are accompanied by a trachea-esophageal fistula, marked often by a gas-filled abdomen due to the communication between the trachea and the esophagus [13]. A trachea-esophageal fistula occurs when there is a failure of the lung bud to separate completely from the foregut, such that the top end of the lower esophagus connects to the windpipe. Esophageal stenosis, in comparison, only occur 1 in 25,000 live births, and is usually located within the middle or lower third of the esophagus [13]. The mechanism leading to esophageal stenosis is much more unclear than that for esophageal atresia, but surgical evidence suggests that it may be due to an incomplete separation of lung bud from primitive foregut, fibromuscular hypertrophy, or from damage to the myenteric plexus.

Intestinal atreasia/stenosis includes atresia/stenosis of the duodenum, jejunum, and ileum, and colon. Duodenal, jejunal, and ileal atresia/stenosis occurs collectively in about 1 in 7,100 livebirths [14]. In general, intestinal atresia stem from the discontinuity of the inside (lumen) of the intestine, completely obstructing the flow of digested food.

Intestinal stenosis also restricts the flow of digested food due to a narrowing of the lumen of the intestine. Jejunal and ileal atresia are thought to stem from vascular compromise or the twisting of the intestine on itself (volvulus), rotational abnormalities, effects on cellular differentiation, or potentially single gene disorders. Familial cases have also been reported for these defects. Duodenal atresia is thought to be due to a failure of the lumen to recanalize during the eighth to twelfth weeks of pregnancy, vascular compromise including volvulus, the annular pancreas causing obstruction, or Ladd's bands (fibrous stalk of tissue attaching to the cecum to the abdominal wall) causing obstruction [14]. Because the pathogenesis of duodenal atresia/stenosis, differs from that of jejunal and ileal atresia/stenosis, it may be advantageous to investigate different risk factors for these defect categories.

Anorectal atresia/stenosis (sometimes referred to as "imperforate anus") occurs in about 1 in 5,000 live births [15]. Anorectal atresia/stenosis can occur in multiple locations on the rectum. Anorectal anomalies stem from faulty separation of the rectum and urogenital system and failure of the anal membrane to rupture. Anorectal atresia/stenosis result from the incomplete formation of the hindgut resulting in imperforate (lack the normal opening) anus with or without fistulous (hollow) connection between the rectum and the perineum (area between anus and posterior part of external genitalia) or urogenital system [15].

This thesis will investigate the association between maternal nutrition (as measured by dietary intake of macronutrients, micronutrients and vitamins, and elements [Table 1]) in the year before pregnancy and risk for certain gastrointestinal atresia/stenosis (esophageal, duodenal, jejunal/ileal, and anorectal) using data from the

NBDPS for pregnancies with estimated dates of delivery in 1997 to 2009.

The findings from these investigations may lead to a better understanding of the role of nutrients in contributing to or preventing these specific birth defects, and may help guide strategies to prevent these defects based on an improved nutrient intake.

CHAPTER II

Review of the Literature

One of the greatest achievements in birth defects epidemiologic research has been the discovery of the association between folic acid use and NTD risk [16]. The strength of this finding and the success of folic acid fortification prevention measures in the U.S. and other countries have encouraged subsequent research on the relationship between folic acid and other birth defects and other facets of maternal nutrition as a pregnancy exposure in relation to adverse birth outcomes, including birth defects [10]. However, few studies have assessed specific nutrients and gastrointestinal atresia/stenosis, as is the goal in our study.

Maternal nutrition and birth defects

A systematic review of studies on the association of nutrition before and during early pregnancy on infant outcomes found evidence supporting the importance of nutritional status before and early pregnancy in reducing risk of birth defects other than NTDs [6]. Analyses using NBPDS data and other study populations have focused on folic acid supplement and multivitamin use in relation to risk for other birth defects. For example, Bitsko, Shaw, and Yuskiv, et al. assessed periconceptional consumption of vitamins containing folic acid and risk for multiple congenital anomalies and observed both significant and null associations between periconceptional vitamin use and multiple congenital anomalies [17-19]. NBDPS studies have also examined maternal nutrition overall as a dietary quality measure. Carmichael et al. measured diet quality based on the summary intake of legumes, grains, fruits and nuts, vegetables, fish, fatty-acids, dairy, meat, sweet, folate, iron, calcium, and calories from fat, and found that risk for

hypospadias was not associated with this diet quality measure [20]. Feldkamp et al. (2014) used the same dietary quality measure, but found that increasing diet quality reduced risk of gastroschisis among Hispanic women [21].

NBDPS studies have also examined the associations between similar exposure profiles (i.e. micronutrients, amino acids, fatty acids, and macronutrients during the year before pregnancy) to our study, but different birth defects. For example, Huber, et al. found that the estimated dietary intake of nitrates, nitrites, and nitrosomes are not significant risk factors for NTD, oral clefts, or limb deficiencies [22]. Feldkamp, et al. (2011) examined the association between average intake of these nutrients and risk of gastroschisis, and whether the association was modified by folic acid supplements, maternal age, or BMI in the same NBDPS study population [23]. The study found that the risk of gastroschisis was only significantly influenced by the highest tertile of copper intake. Yang, et al. also found increased risks for congenital diaphragmatic hernias (CDH) for lower intakes of choline, cysteine, methionine, and protein, and decreased risks for higher intake of choline [24].

Gastrointestinal atresia/stenosis and other exposures

Minimal research has been done on specific nutrients and gastrointestinal atresia/stenosis. Related to our interest in anorectal atresia/stenosis, Myers et al. examined the association between folic acid supplementation and imperforate anus in China [25]. The study found no association between folic acid supplementation and imperforate anus controlling for region, education, and occupation. However, Gilboa, et al. found a positive association between the third quartile of vitamin E intake and anorectal atresia/stenosis in a spectrum study of maternal intake of vitamin E and birth

defects in NBDPS [26].

Data from the NBDPS and other study populations have also been used to examine gastrointestinal atresia/stenosis and their associations with exposures other than nutrients. The associations found in these studies will guide our covariate selection in subsequent analyses. For instance, in a NBDPS analysis, no association was observed between anorectal atresia and alcohol consumption; a small elevated risk of anorectal atresia/stenosis was observed with maternal cigarette smoking during the periconceptional period, as well as with environmental tobacco smoke (ETS) and higher caffeine intake [27]. A systematic review and meta-analysis examining parental risk factors and anorectal malformations found consistently increased observed risks for paternal smoking, maternal overweight status, obesity, and diabetes [28]. Increased risk was not observed for maternal smoking and alcohol consumption and the reported risks associated with illicit drug use were inconclusive. An analysis of NBDPS data observed a positive significant association between odds of anorectal atresia/stenosis and obese mothers [5].

With regards to esophageal atresia/stenosis, a NBDPS study examined periconceptional cigarette smoking and alcohol consumption and esophageal astresia/stenosis with and without trachea-esophageal fistula [29]. Weak associations were observed between any periconceptional exposure to smoking and each case phenotype, with the highest risk for mothers who smoked cigarettes and whose child did not have an isolated atresia. Smoking and alcohol as a combined exposure also had a weak association with esophageal atresia/stenosis with and without tracheo-esophageal fistula. A case-control population-based study in Sweden also found no association

between maternal tobacco smoking during early pregnancy and risk of esophageal atresia [30]. In addition, there was no significant association between maternal BMI and risk of esophageal atresia or maternal SES and risk of esophageal atresia.

Currently, little literature addresses the association between gastrointestinal atresia/stenosis and specific nutrients. Like NBDPS, the primary limitation of these studies is the reliance on maternal recall and the retrospective ascertainment of nutritional data. In addition, NBPDS and some studies used abbreviated food frequency questionnaires, further introducing opportunity for measurement error. While these limitations exist, there is no "best method" to assess individual nutrients during prepregnancy and early pregnancy. Measuring dietary intake in any population is difficult due to the reliance on recall and the assumption of unchanging dietary habits. Obtaining this nutritional information from pregnant women during the critical exposure window and relying on their dietary habits to remain consistent for the duration of their pregnancy only increases these challenges. Thus, we are limited to these data and methods available. To address some of these concerns, we will utilize the strengths of the NBPDS to examine average nutrient intakes and the association with these gastrointestinal atresia/stenosis adjusting for total energy intake.

CHAPTER III

Methodology

This analysis uses data from the National Birth Defects Prevention Study (NBDPS) in collaboration with the Georgia study center, located within the National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention (CDC) and with approval from the Centers for Birth Defects Research and Prevention (CBDRP) Data Sharing Committee. NBDPS uses data from existing population-based birth defects surveillance systems in Arkansas, California, Georgia, Iowa, Massachusetts, New York, New Jersey, North Carolina, Texas, and Utah [31] (Figure 2). IRB approval was obtained from the CDC as well as each study center. We focused our analysis on esophageal, duodenal, jejunal/ileal, and anorectal atresia/stenosis identified by Centers beginning with estimated dates of delivery of October 1, 1997 and ending with estimated dates of delivery on December 31, 2009.

Case ascertainment methods differed somewhat across Centers; further specifics are described elsewhere [31]. These differences include treatment of stillbirths and terminations and size of catchment areas. For example, some Centers only ascertain cases from liveborn infants, while some Centers also include stillborn infants and/or prenatally diagnosed and electively terminated pregnancies. Dates when each birth outcome was ascertained for each Center are provided (Table 2). We will include cases with all pregnancy outcomes (i.e., live born, stillborn, and elective termination) in our analysis. In addition, some Centers ascertain cases statewide and some from only select areas and counties (Figure 3) [31].

The categories of gastrointestinal atresia/stenosis included in the analysis were

identified based on detailed case definition criteria developed collaboratively by clinical geneticists at each Center [32]. Information used to determine case eligibility and classification was obtained from hospital reports and medical records. Esophageal atresia were classified as all cases diagnosed by a prenatal ultrasound, x-ray after placement of a radiopaque feeding tube or contrast material, surgical notes, or autopsy. Cases of jejunal/ileal atresia/stenosis were classified as stenosis or atresia of the small intestine confirmed at the time of surgical repair or autopsy, and cases with duodenal webs were classified as a type of duodenal atresia; cases with both isolated and multiple stenotic and/or atretic segments are also included in the small intestinal/duodenal atresia classifications. Anorectal atresia/stenosis cases were classified according to the fistula positioning in associated muscles. Clinical geneticists at each center reviewed each case entry to confirm the case definition and standardize the case coding. Controls were liveborn infants with no major birth defects randomly selected based on the proportion of number of births in the same geographic area from which the cases were ascertained, using either birth certificates or hospital birth logs; the catchment areas can be seen in Figure 3.

Case and control mothers were mailed introductory packets no earlier than six weeks after the infant's estimated date of delivery. The packets (available in both English and Spanish) contained an introductory letter, a list of frequently asked questions, a "Rights of Research Subjects" information sheet, a monetary incentive, a response list for items included in the subsequent interview, and a calendar that covers the duration of the pregnancy. About ten days after the packet was mailed, the mothers were contacted by a trained interviewer to answer any questions and to conduct the interview or schedule

the interview for a later date. The interviews lasted about one hour and were conducted using a computer-assisted telephone interview (CATI). The questions asked mothers about demographic and lifestyle factors and experiences during pregnancy (e.g., chronic medical conditions, medication use, infections, nutrition, and cigarette and alcohol use) that could potentially be associated with birth defect risk, focusing on exposures that occurred from three months before conception through the end of pregnancy. The interview could be completed in one or several sessions and was targeted for completion within six months of the expected date of delivery but no earlier than 6 weeks and no later than 24 months of the expected date of delivery.

The estimates of nutrient intake used in this analysis come from data obtained in three separate sections of the CATI. Mothers were administered a 58-item food frequency questionnaire (FFQ) based on a shortened Willett/Harvard food frequency questionnaire [33]. Mothers were asked about their average intake of these items during the year prior to their pregnancy. Soda intake in the year prior to pregnancy was asked about separately from the FFQ, but was also included in the nutrient calculations. The other data incorporated into the nutrient calculations came from questions asking mothers about their intake of cereal and food supplements like protein powder during the three months before through the end of pregnancy; only foods reported in the 3 months prior to pregnancy were included in the nutrient calculations. Daily nutrient data values were calculated based on reported intake of foods by using the USDA National Nutrient Database for Standard Reference version 25 [34]. Of note, intake of single vitamins or multivitamins was not incorporated into the nutrient estimates. We focused on three categories of nutrients: macronutrients, micronutrients/vitamins, and elements (Table 1).

All nutrient values were categorized as quartiles based on the nutrient's distribution among control mothers to account for inaccuracies in the estimates of the absolute nutrient values (Table 3). We used the lowest quartile of intake as the reference group. Total energy intake (kcal) was also estimated and adjusted for in the analyses. Mothers with total energy intake less than 500 or greater than 5000 kcal and mothers with more than three missing responses to FFQ questions were excluded from the analyses. Due to the known relationship between pregestational diabetes and some of the categories of gastrointestinal atresia/stenosis included in the analysis, women with documented type I or type II diabetes diagnosed prior to pregnancy were excluded [35, 36].

The maternal characteristics of interest as potential confounders were decided *a priori* based on existing literature [27-30]. The maternal characteristics of primary interest were age, race/ethnicity, education, pre-pregnancy body mass index (BMI) (weight in kilograms divided by height in meters squared), first trimester nausea/vomiting, and use of folic acid supplements. Study Center was also examined as a potential confounder and effect modifier. Age was categorized as less than 25 years old, 25-29 years old (reference group), 29-34 years old, and more than 35 years old; race was categorized as white non-Hispanic (reference group), black non-Hispanic, Hispanic, and other; maternal education was categorized as less than a high school education (reference group), high school graduate, post-high school degree; maternal BMI was categorized as not obese (BMI<30; reference group) and obese; and number of previous live births was categorized into no previous live births (reference group) or ≥1 previous live births [37]. Use of folic acid supplements was defined as any use of folic acid supplements in the months prior to pregnancy through the first month of pregnancy or no

supplement use during that time frame. Chi-square tests of association were performed to assess differences in the distribution of characteristics between case and control mothers. In addition, crude odds ratios with 95% Wald confidence intervals were estimated for each covariate to estimate the association between each category gastrointestinal atresia/stenosis and the covariate.

Adjusted odds ratios and corresponding 95% Wald confidence intervals were estimated to estimate the associations between risk for each category of gastrointestinal atresia/stenosis and quartile of average nutrient intake using multivariable logistic regression and SAS 9.3 [38]. We modeled each gastrointestinal atresia/stenosis outcome separately and adjusted for the maternal characteristics described above, Study Center, and average total energy intake. Because we are evaluating an outcome that is rare the odds ratio can approximate relative risk ratio.

CHAPTER IV

Results

Maternal characteristics

Our initial sample consisted of 658 esophageal atresia/stenosis cases, 197 duodenal atresia/stenosis cases, 430 jejunal/ileal atresia/stenosis cases, and 951 anorectal atresia/stenosis cases, and 10,200 controls. After the exclusions, we used 612 esophageal atresia/stenosis cases, 189 duodenal atresia/stenosis cases, 401 jejunal/ileal atresia/stenosis cases, 863 anorectal atresia/stenosis cases, and 9,632 controls in our analyses. Maternal characteristics for these case and control groups and differences between the groups can be seen in Table 4.

Mothers of esophageal atresia/stenosis cases were more likely to be ≥30 years old compared to control mothers. Mothers of jejunal/ileal atresia/stenosis cases were more likely to be ≥ 35years old than control mothers, while mothers of anorectal atresia/stenosis cases were more likely to be younger than 25 years old than control mothers.

The race/ethnicity distribution for case mothers was significantly different than the control mothers for all gastrointestinal atresia/stenosis case groups except for duodenal atresia/stenosis. Mothers of esophageal atresia/stenosis cases were more often non-Hispanic white, mothers of jejunal/ileal atresia/stenosis cases were more often non-Hispanic black or Hispanic, and mothers of anorectal atresia/stenosis cases were more often Hispanic compared to control mothers. Mothers of esophageal atresia/stenosis cases more often had a post-high school degree than control mothers, while mothers of duodenal, jejunal/ileal, and anorectal atresia/stenosis cases were more likely to have less

than a high school education than control mothers.

Maternal pre-pregnancy obesity was associated with increased odds of both jejunal/ileal and anorectal atresia/stenosis. Mothers of esophageal and duodenal atresia/stenosis cases were likely to have no previous live births than control mothers. Mothers of all the gastrointestinal atresia/stenosis cases appeared to be less likely to have nausea and/or vomiting during the first trimester than control mothers. Mothers of esophageal atresia/stenosis cases were more likely to use folic acid supplements during the periconceptional period than control mothers.

Associations between average nutrient intake and gastrointestinal atresia/stenosis

We observed few meaningful strong associations between quartile of nutrient intake and risk for any of the categories of gastrointestinal atresia/stenosis. (Table 5; Figure 4 A-L). A possible linear trend in odds for esophageal atresia/stenosis risk was observed for fiber, with decreasing odds associated with higher quartiles of intake. For fat and carbohydrates, the highest quartile of intake was borderline significantly associated with lower odds of duodenal atresia/stenosis.

Mothers with Vitamin B6 intakes greater than the first quartile had borderline significant lower odds of esophageal atresia/stenosis than mothers with intakes in the lowest quartile. A possible linear trend was observed for Vitamin A intake and duodenal atresia/stenosis, with decreasing odds of duodenal atresia/stenosis associated with increasing quartiles of Vitamin A intake. Mothers with Vitamin C intakes greater than the first quartile had lower odds of duodenal atresia/stenosis than mothers with the lowest quartile of intake; mothers with the highest quartile of intake of Vitamin C had borderline significant odds of duodenal atresia/stenosis than mothers with the lowest quartile of

intake. Mothers with the highest quartile of intake of Vitamin E also had significant lower odds of duodenal atresia/stenosis compared to mothers with the lowest quartile of intake. Mothers with intakes of beta-carotene greater than the lowest quartile of intake had moderately lower odds of duodenal atresia/stenosis than mothers with the lowest quartile of beta-carotene intake. Vitamin B6 and riboflavin showed a modest possible linear trend with decreasing odds of anorectal atresia/stenosis and higher quartiles of intake. Mothers with intakes of Vitamin B1, niacin, and folate in the highest quartile had lower odds of anorectal atresia/stenosis than mothers with intakes of these vitamins/micronutrients in the lowest quartile. Similarly, mothers with intakes of Vitamin B12, Vitamin C, and Vitamin E greater than the lowest quartile had lower odds of anorectal atresia/stenosis than mothers with the lowest quartile of intake.

The odds of esophageal atresia/stenosis were lower for mothers in the 2nd through 4th quartiles of intake for magnesium. A significantly lower odds of duodenal atresia/stenosis was observed for mothers with the highest quartile of magnesium intake (OR = 0.42, 95% CI [0.19, 0.91]). Reduced odds of anorectal atresia/stenosis was associated with intake in the highest quartile for iron, zinc, copper, and magnesium; a decreased odds was associated with calcium intake in the highest two quartiles.

CHAPTER V

Conclusions, Implications, and Recommendations

Our findings do not support clear associations between the examined macronutrients, micronutrients/vitamins, and elements, and risk for esophageal, duodenal, jejunal/ileal, or anorectal atresia/stenosis. If associations exist, they are likely to be modest such that with our sample size we were unable to detect them. However, some visual trends between risk for the gastrointestinal atresia/stenosis outcomes and quartiles of nutrient intake suggest that further investigation might be warranted.

Our crude analyses showed that the maternal characteristics associated with esophageal and anorectal atresia/stenosis risk were generally consistent with previous studies [27-30]. In line with Myer, et al.'s findings, we also found no association between anorectal atresia/stenosis risk and folate supplement use in our crude analyses [25].

Although we identified possible patterns between quartile of nutrient intake and odds of gastrointestinal atresia/stenosis, no dietary recommendations can be made based on these findings. Our study should be replicated, perhaps with a different diet metric to further investigate the associations and possible trends.

The main strength of this study is the data source. NBDPS is a large, population-based, multi-center case-control study; thus, data from this study can be used to analyze rare outcomes such as gastrointestinal atresia/stenosis from a diverse population. The use of the CATI and other standardized methods for case and exposure ascertainment allows for the minimization of information biases.

Our results should be interpreted within the limitations of our analysis. Our

examination of maternal nutrition by individual nutrient may have contributed to our finding of null associations between nutrient intake and gastrointestinal atresia/stenosis. Previous NBPDS studies, namely by Carmichael et al. and Feldkamp et al., assessed maternal nutrition and birth defect risk using a dietary quality measure [20, 21]. Their examination of maternal diet in its entirety, rather than by individual nutrient, may be more relevant to examining maternal diet and gastrointestinal atresia/stenosis.

The nutrient data also relies entirely on maternal recall from the maternal interview. The nutrition information is gathered as part of an overall extensive survey of pregnancy exposures through a shortened food frequency questionnaire. While noting these limitations, it should be considered that there is no established "gold standard" method to collect nutrient data during pregnancy, especially during the short time frame around conception through the beginning of pregnancy when these exposures are of greatest interest for their potential impact on the development of birth defects. In addition, while extensive covariate information was available, unmeasured confounding might still be present.

There are also challenges in the classification of cases of gastrointestinal astresia/stenosis. The NBDPS clinical review and classification process is thorough and involves validation by multiple clinicians, but whether a given instance of gastrointestinal atresia/stenosis occurs as an isolated defect or part of a complex association of multiple defects can be challenging to determine. While the cases of gastrointestinal atresia/stenosis we examined could be co-occurring and related, the known embryology of gastrointestinal atresia/stenosis suggest that they are etiologically different and hence warrants separate analyses [13-15]. In this respect, performing analyses stratifying the

cases of gastrointestinal atresia/stenosis also based on whether they are isolated or complex may be warranted.

Additional methodological considerations could be made with more data as well. For instance, our current odds ratios plots suggest possible trends and understanding of these potential trends can improve with the addition of more data and may justify the statistical investigation of trend patterns. Future studies may also look further into study Center, perhaps adding site location to the regression model as a random effect rather than as a covariate, and performing spatial analyses. In addition, there are multiple methodologies to adjust models for total energy intake. While we followed past NBDPS studies and utilized the simplest method of adding average total energy intake as a covariate in the model, other methods, such as the residual method, where individual nutrient intakes are regressed on their total energy intakes, would be worthy to investigate [39].

While we observed few association between macronutrients, micronutrients/vitamins, and elements and esophageal, duodenal, jejunal/ileal, and anorectal atresia/stenosis, the high prevalence of obesity in the United States and the associated dietary patterns suggest that dietary intake in early pregnancy is a relevant and important exposure that deserves further research attention.

Tables and Figures

Table 1.
Maternal nutrients examined with data available from the National Birth Defects Prevention Study (NBPDS) 1997-2009

Macronutrients
Carbohydrates
Cholesterol
Fat
Monosaturated Fatty Acids
Polyunsaturated Fatty Acids
Protein
Saturated Fatty Acids
Micronutrients/Vitamins
Beta-carotene
Choline
Folate
Methionine
Vitamin A (retinol, carotenoids)
Vitamin B1 (thiamin)
Vitamin B12 (cobalamin)
Vitamin B2 (niacin)
Vitamin B2 (riboflavin)
Vitamin B6 (pyridoesine)
Vitamin C
Vitamin E
Elements
Calcium
Copper
Iron
Magnesium
Selenium
Zinc

Figure 1.
Prevalence of Self-Reported Obesity Among U.S. Adults, Behavior Risk Factor Surveillance System 2013 [40]

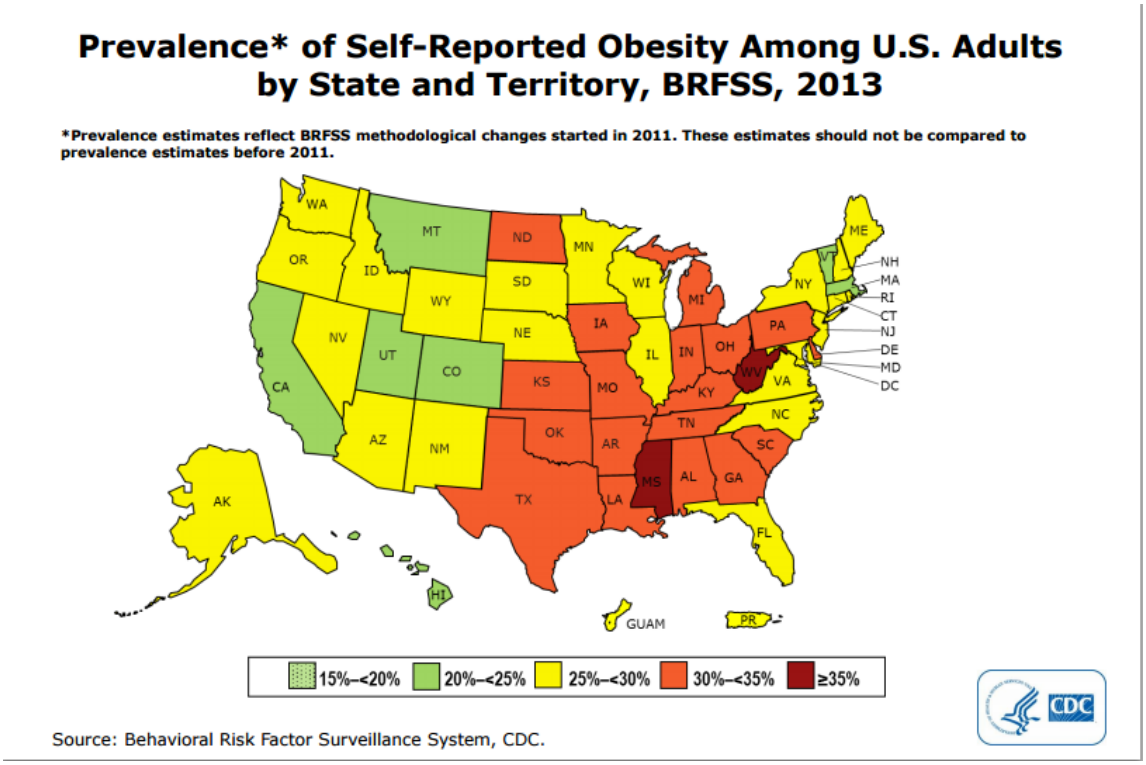
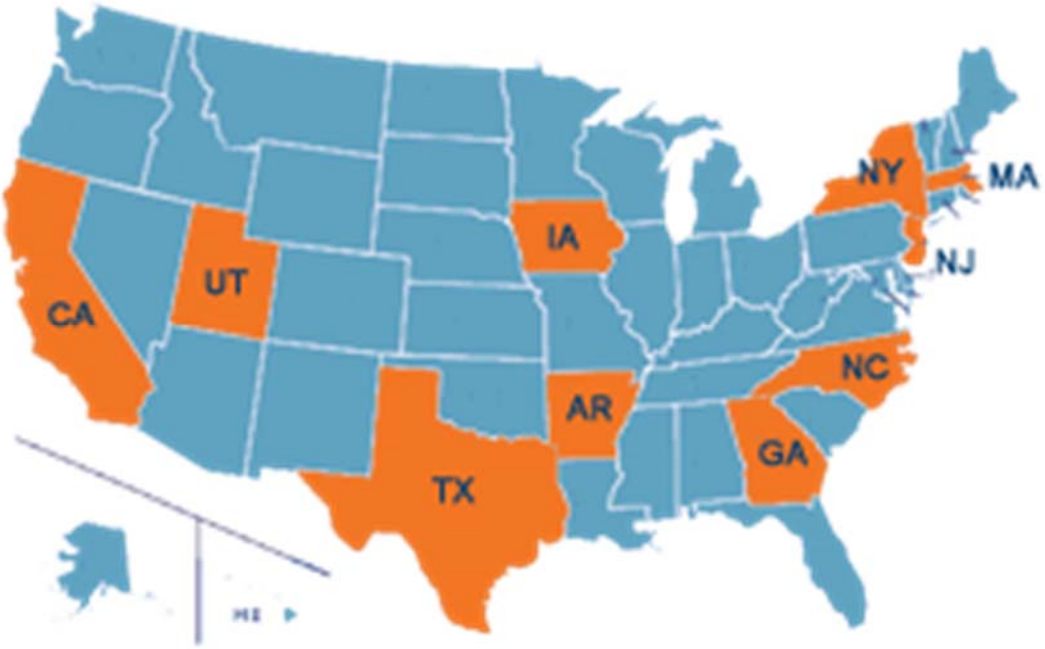


Figure 2.
Map of National Birth Defects Prevention Study (NBPDS) study locations[1,2] [41]



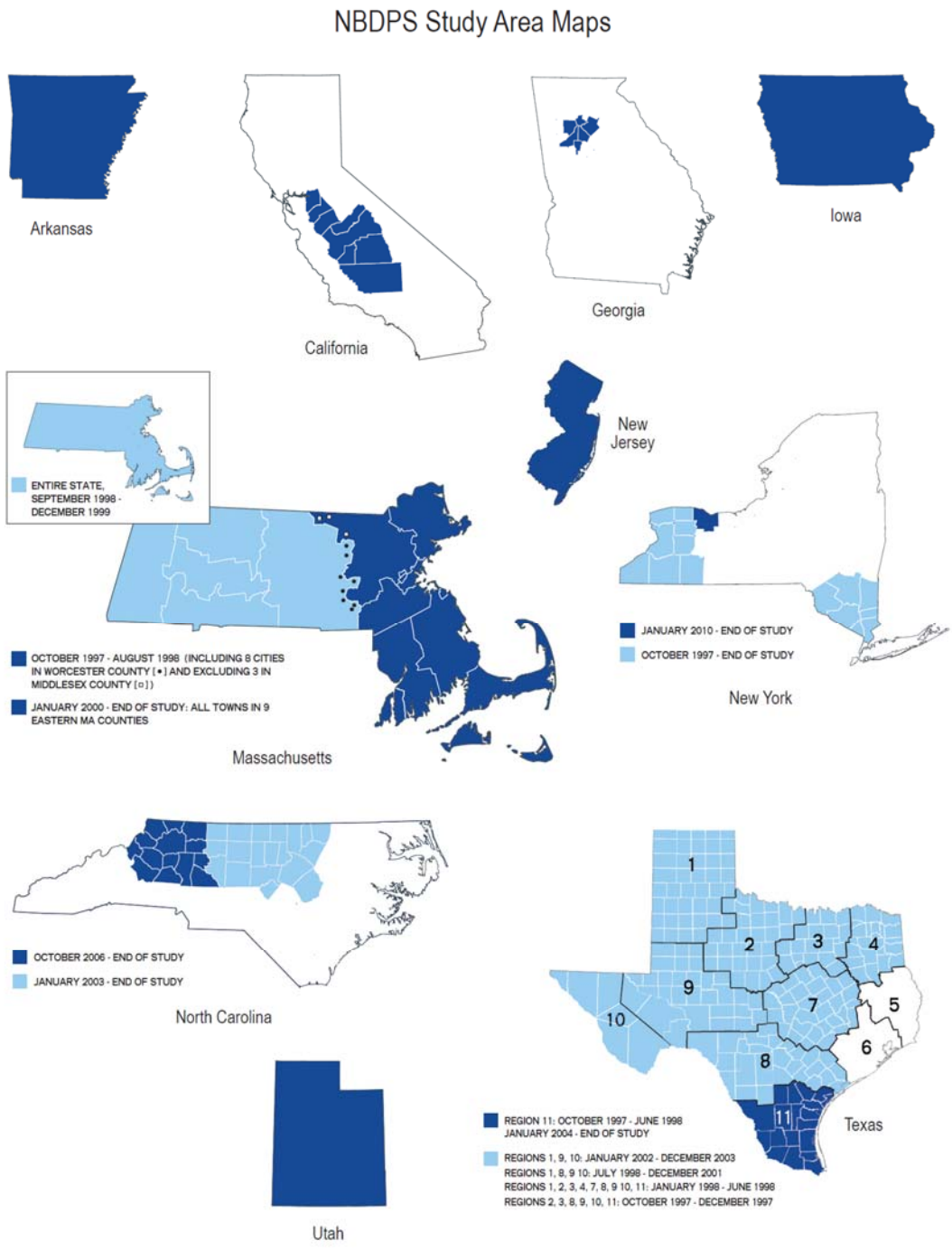
[1]NBDPS study locations highlighted in orange
[2]Data contribution dates via maternal interview (through December 2009): Arkansas (AR) March 1998-Decemeber 2009; California (CA) December 1997-December 2009; Georgia (GA) October 1997-December 2009; Iowa (IA) October 1997-December 2009; Massachusetts (MA) October 1997-December 2009; North Carolina (NC) January 2003-December 2009; New Jersey (NJ) January 2003-June 2003; New York (NY) October 1997-January 2004 (data collection interrupted in part of 2002 and all of 2003); Texas (TX) October 1997-July 2007 and July 2008-December 2009; Utah (UT) January 2003-December 2009

Table 2.
Dates prenatally diagnosed cases, elective pregnancy terminations, and stillbirths initially captured in National Birth Defects Prevention Study (NBPDS) by Study Center[1,2]

NBDPS Center	Prenatally Diagnosed Cases	Induced abortions	Stillbirths	Newborn Screening Bloodspots
AR	January1998 (Began Ascertainment)	January 1998 (Began Ascertainment)	January 1998 (Began Ascertainment)	Not applicable
CA	January 2004 (DOB)	December 1997 (DOB)	December 1997 (DOB)	Not applicable
GA	January 2000	January 1999	October 1997	Not applicable
IA	October 1997 (EDD)	October 1997 (EDD)	October 1997 (EDD)	Not applicable
MA	January 2011 (EDD)	January 2011 (EDD)	October 1997 (DOB)	November 2013 (Date first bloodspot consent forms mailed retrospectively (1997-2011 births) with request letter to participants.) Some exclusions: • Spanish-speaking (may include later) • Present out-of-state address on file (may include later) • Born out of state-MA resident (includes born in RI hospitals) • "Do not contact family", "ineligibles", or no valid address. • Study infant death (checked from birth to present) • Reportable fetal death, stillbirth, or other pregnancy loss • Hard refusals (for biologics, recollects or dry brush project).
NC	January 2003 (EDD)	January 2003 (EDD)	January 2003 (EDD)	March 2004 (Date first bloodspot consent forms mailed in buccal kits). Excluded therapeutic abortions, stillbirths and deceased children.
NJ	January 1, 1998 (Began Ascertainment)	Never	Never	
NY	January 2000 (EDD)	January 2000 (EDD)	January 2000 (EDD)	April 2011
TX	August 2010 (Began Ascertainment)	October 1997 (DOB)	October 1997 (DOB)	Not applicable
UT	January 2003 (DOB)	January 2003 (DOB)	January 2003 (DOB)	January 2006 (DOB)

[1]Figure used with permission from Dr. Sarah Tinker and the Georgia study center
[2]Arkansas (AR); California (CA); Georgia (GA); Iowa (IA); Massachusetts (MA); North Carolina (NC); New Jersey (NJ); New York (NY); Texas (TX); Utah (UT); Date of birth (DOB); Estimated date of delivery (EDD)

Figure 3.
National Birth Defects Prevention Study (NBPDS) Study Area Maps[1],[2]



[1] Regions shaded in blue are regions where cases and controls were ascertained; different shades of blue refer to different time periods of ascertainment

[2] Figure used with permission from Dr. Sarah Tinker and the Georgia study center

Table 3.
Distribution of self-reported nutrients in the year before pregnancy among control mothers, National Birth Defects Prevention Study (NBDPS) 1997-2009

Macronutrients												
	Protein (g)	Fat (g)	Carbohydrates (g)	Dietary fiber (g)	Fatty acids (mono-saturated) (g)	Fatty acids (polyunsaturated) (g)	Fatty acids (saturated) (g)	Cholesterol (mg)				
25th Percentile	50.44	34.51	150.25	10.98	12.04	4.92	13.29	150.16				
Median	65.72	46.09	203.17	15.94	16.37	6.83	18.03	208.57				
75th Percentile	84.9	61.17	280.38	23.52	22.06	9.4	24.12	290.66				
Micronutrients/Vitamins												
	Vitamin A (µg)	Vitamin B1 (thiamin) (mg)	Vitamin B2 (riboflavin) (mg)	Vitamin B2 (niacin) (mg)	Vitamin B6 (pyridopsine) (mg)	Vitamin B12 (cobalamin) (µg)	Folate (µg)	Vitamin C (mg)	Choline (mg)	Vitamin E (mg)	Beta-carotene (µg)	Methionine
25th Percentile	459.02	0.85	1.31	13.96	1.45	3.25	321.04	59.42	218.15	3.43	1165.3	1.07
Median	669.03	1.15	1.79	18.41	1.97	4.79	468.89	101.11	293.19	4.91	2170.75	1.41
75th Percentile	966.58	1.56	2.45	24.39	2.67	7	674.64	154.94	394.23	7.16	3770.2	1.85
Elements												
	Iron (mg)	Zinc (mg)	Copper (mg)	Calcium (mg)	Magnesium (mg)	Selenium (µg)						
25th Percentile	8.37	7.77	0.69	521.8	175.78	57.88						
Median	12.32	10.4	0.937	760.96	232.63	75.91						
75th Percentile	17.46	13.8	1.32	1077.8	311.99	99.56						

Table 4.
Characteristics of mothers of gastrointestinal atresia/stenosis cases and controls, National Birth Defects Prevention Study (NBPDS) 1997-2009

		Esophageal atresia/stenosis			Duodenal atresia/stenosis			Jejunal/Ileal atresia/stenosis			Anorectal atresia/stenosis		
	Controls [N (%)]	Cases [N (%)]	Crude Odds Ratio (95% CI)	p-value[1]	Cases [N (%)]	Crude Odds Ratio (95% CI)	p-value[1]	Cases [N (%)]	Crude Odds Ratio (95% CI)	p-value[1]	Cases [N (%)]	Crude Odds Ratio (95% CI)	p-value[1]
Total (N)	9632	612			189			401			863		
Maternal Characteristics													
Maternal age (years)													
< 25	3551 (36.87)	187 (30.56)	0.96 (0.77, 1.20)	<0.01	77 (40.74)	1.34 (0.92, 1.94)	0.49	164 (40.90)	1.15 (0.90, 1.47)	0.0158	333 (38.59)	1.17 (0.98, 1.39)	0.34
25-29	2712 (28.16)	148 (24.18)	1		44 (23.28)	1		109 (27.18)	1		218 (25.26)	1	
30-34	2300 (23.88)	171 (27.94)	1.36 (1.09, 1.71)		47 (24.87)	1.26 (0.83, 1.91)		72 (17.96)	0.78 (0.57, 1.05)		213 (24.68)	1.15 (0.95, 1.40)	
>34	1069 (11.10)	106 (17.32)	1.82 (1.40, 2.35)		21 (11.11)	1.21 (0.72, 2.05)		56 (13.97)	1.30 (0.94, 1.81)		99 (11.47)	1.15 (0.90, 1.48)	
Maternal race/ethnicity													
Non-Hispanic White	5673 (58.94)	413 (67.48)	1	<0.01	100 (52.91)	1	0.2097	183 (45.64)	1	<0.01	454 (52.67)	1	<0.01
Non-Hispanic Black	1047 (10.88)	32 (5.23)	0.42 (0.29, 0.60)		28 (14.81)	1.52 (0.99, 2.32)		61 (15.21)	1.81 (1.34, 2.43)		88 (10.21)	1.05 (0.83, 1.33)	
Hispanic	2229 (23.16)	120 (19.61)	0.74 (0.60, 0.91)		49 (25.93)	1.25 (0.88, 1.76)		127 (31.67)	1.77 (1.40, 2.23)		251 (29.12)	1.41 (1.20, 1.65)	
Other	676 (7.02)	47 (7.68)	0.95 (0.70, 1.30)		12 (6.35)	1.01 (0.55, 1.84)		30 (7.48)	1.38 (0.93, 2.04)		69 (8.00)	1.27 (0.98, 1.66)	
Maternal Education													
< High school	1602 (16.76)	89 (14.57)	1	<0.01	41 (21.93)	1	0.17	92 (23.06)	1	<0.01	165 (19.30)	1	<0.01
High school graduate	4532 (47.41)	258 (42.23)	1.02 (0.80, 1.31)		82 (43.85)	0.71 (0.48, 1.03)		189 (47.37)	0.73 (0.56, 0.94)		430 (50.29)	0.92 (0.76, 1.11)	
Post-high school degree	3426 (35.84)	264 (43.21)	1.39 (1.08, 1.78)		64 (34.22)	0.73 (0.49, 1.08)		118 (29.57)	0.60 (0.45, 0.79)		260 (30.41)	0.74 (0.60, 0.90)	
Maternal BMI													
Not Obese (≤ 29)	7512 (81.41)	472 (80.68)	1	0.6603	142 (80.68)	1	0.8	296 (77.89)	1	0.0849	626 (77.00)	1	<0.01
Obese (> 29)	1715 (18.59)	113 (19.32)	1.05 (0.85, 1.30)		34 (19.32)	1.05 (0.72, 1.53)		84 (22.11)	1.24 (0.97, 1.59)		187 (23.00)	1.31 (1.10, 1.55)	
Previous pregnancies ending in live birth													
0	2863 (29.73)	235 (38.40)	1	<0.01	72 (38.10)	1	0.01	127 (31.67)	1	0.4	256 (29.66)	1	0.97
≥ 1	6768 (70.27)	377 (61.60)	0.68 (0.57, 0.80)		117 (61.90)	0.69 (0.51, 0.92)		274 (68.33)	0.91 (0.74, 1.13)		607 (70.34)	1.00 (0.86, 1.17)	
Study Center													
Arkansas	1231 (12.78)	73 (11.93)	0.86 (0.60, 1.22)	<0.01	16 (8.47)	0.82 (0.39, 1.72)	0.02	41 (10.22)	1.19 (0.71, 2.00)	<0.01	129 (14.95)	1.60 (1.15, 2.22)	<0.01
California	1086 (11.27)	62 (10.13)	0.82 (0.57, 1.19)		27 (14.29)	1.57 (0.81, 3.07)		76 (18.95)	2.50 (1.56, 4.03)		125 (14.48)	1.75 (1.26, 2.44)	
Georgia	992 (10.30)	67 (10.95)	0.97 (0.68, 1.40)		23 (12.17)	1.91 (0.99, 3.69)		88 (13.97)	1.95 (1.18, 3.20)		89 (10.31)	1.37 (0.96, 1.94)	
Iowa	1068 (11.09)	47 (7.68)	0.63 (0.43, 0.94)		15 (7.94)	0.89 (0.42, 1.88)		36 (8.98)	1.21 (0.71, 2.05)		57 (6.60)	0.81 (0.55, 1.19)	
Massachusetts	1155 (11.99)	97 (15.85)	1.21 (0.86, 1.70)		23 (12.17)	1.26 (0.63, 2.50)		46 (11.47)	1.42 (0.86, 2.37)		104 (12.05)	1.37 (0.98, 1.93)	
New Jersey	564 (5.86)	53 (8.66)	1.36 (0.92, 2.00)		11 (5.82)	1.23 (0.55, 2.78)		39 (9.73)	2.47 (1.46, 4.19)		74 (8.57)	2.00 (1.40, 2.89)	
New York	822 (8.53)	60 (9.80)	1.05 (0.72, 1.53)		9 (4.76)	0.69 (0.29, 1.63)		27 (6.73)	1.17 (0.67, 2.07)		54 (6.26)	1.00 (0.68, 1.48)	
North Carolina	759 (7.88)	40 (6.54)	0.76 (0.50, 1.15)		23 (12.17)	1.92 (0.96, 3.81)		22 (5.49)	1.04 (0.57, 1.88)		59 (6.84)	1.18 (0.81, 1.74)	
Texas	1132 (11.75)	56 (9.15)	0.71 (0.49, 1.04)		22 (11.64)	1.23 (0.62, 2.46)		37 (9.23)	1.17 (0.69, 1.98)		118 (13.67)	1.59 (1.14, 2.22)	
Utah	823 (8.54)	57 (9.31)	1		13 (6.88)	1		23 (5.74)	1		54 (6.26)	1	
First trimester nausea and/or vomiting													
Yes	6709 (69.65)	388 (63.40)	0.75 (0.63, 0.89)	<0.01	116 (61.38)	0.69 (0.51, 0.92)	0.01	267 (66.58)	0.86 (0.70, 1.07)	0.1711	580 (67.21)	0.89 (0.76, 1.03)	0.11
No	2904 (30.15)	224 (36.60)	1		73 (38.62)	1		134 (33.42)	1		283 (32.79)	1	
Use of folate supplement*													
Yes	5003 (51.96)	350 (57.19)	1.23 (1.05, 1.46)	0.01	93 (49.21)	0.90 (0.67, 1.19)	0.45	191 (47.63)	0.84 (0.69, 1.03)	0.0889	429 (49.77)	0.92 (0.80, 1.05)	0.22
No (or other time)	4625 (48.04)	262 (42.81)	1		96 (50.79)	1		210 (52.37)	1		433 (50.23)	1	

[1] p-values obtained from Chi-square tests of association; * use prior to pregnancy or during first month of pregnancy

Table 5.
Association between gastrointestinal atresia/stenosis and self-reported maternal nutrient intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009

	Esophageal atresia/stenosis		Duodenal atresia/stenosis		Jejunal/Ileal atresia/stenosis		Anorectal atresia/stenosis	
Nutrient categories	No. Cases	Adjusted OR* (95% CI)	No. Cases	Adjusted OR* (95% CI)	No. Cases	Adjusted OR* (95% CI)	No. Cases	Adjusted OR* (95% CI)
Total	612		189		401		863	
Macronutrients								
Protein (g)								
< 50.44	172	Reference	57	Reference	108	Reference	237	Reference
50.44 - 65.72	147	0.817 (0.62,1.07)	39	0.864 (0.53,1.42)	82	0.829 (0.58,1.17)	220	0.947 (0.75,1.19)
65.72-84.90	146	0.87 (0.62,1.22)	50	1.139 (0.64,2.02)	99	1.012 (0.67,1.53)	206	0.955 (0.71,1.27)
> 84.90	147	0.888 (0.60,1.32)	43	0.936 (0.44,1.97)	112	1.013 (0.64,1.61)	200	0.891 (0.63,1.26)
Fat (g)								
< 34.51	164	Reference	59	Reference	120	Reference	231	Reference
34.51 - 46.09	153	1.07 (0.81,1.41)	50	0.956 (0.60,1.52)	78	0.695 (0.49,0.98)	229	1.052 (0.84,1.32)
46.09 - 61.17	146	1.082 (0.76,1.54)	46	0.99 (0.54,1.80)	103	0.786 (0.53,1.16)	211	0.981 (0.73,1.32)
> 61.17	149	1.235 (0.82,1.85)	34	0.5 (0.23,1.09)	100	0.979 (0.60,1.58)	192	0.92 (0.64,1.31)
Carbohydrates (g)								
< 150.25	171	Reference	60	Reference	101	Reference	208	Reference
150.25 - 203.17	166	1.046 (0.77,1.42)	45	0.855 (0.49,1.48)	88	1.158 (0.77,1.73)	252	1.328 (1.02,1.73)
203.17 - 280.38	148	0.961 (0.62,1.48)	46	0.97 (0.47, 2.00)	89	1.019 (0.59,1.77)	200	1.045 (0.71,1.53)
> 280.38	127	0.907 (0.56,1.47)	38	0.481 (0.20,1.13)	123	1.262 (0.74,2.14)	203	0.976 (0.65,1.47)
Dietary fiber (g)								
< 10.98	176	Reference	55	Reference	104	Reference	226	Reference
10.98 -15.94	154	0.81 (0.63,1.04)	36	0.795 (0.49,1.28)	80	0.716 (0.51,1.00)	227	1.001 (0.81,1.24)
15.94 - 23.52	147	0.759 (0.56,1.02)	52	1.155 (0.70,1.90)	96	0.952 (0.66,1.37)	206	0.857 (0.66,1.11)
> 23.52	135	0.642 (0.44,0.94)	46	0.696 (0.35,1.40)	121	0.908 (0.58,1.42)	204	0.769 (0.55,1.08)
Fatty acids (mono-saturated) (g)								
< 12.04	174	Reference	55	Reference	111	Reference	229	Reference
12.04 - 16.37	141	0.924 (0.70,1.22)	56	1.112 (0.71,1.74)	88	0.797 (0.57,1.12)	230	1.041 (0.83,1.30)
16.37 - 22.06	146	0.79 (0.50,1.24)	42	0.972 (0.54,1.76)	100	0.84 (0.57,1.24)	205	0.962 (0.73,1.27)
> 22.06	151	0.939 (0.67,1.31)	36	0.678 (0.31,1.46)	102	1.065 (0.67,1.70)	199	0.888 (0.63,1.25)

Table 5 (cont.)

Fatty acids (polyunsaturated) (g)								
< 4.92	161	Reference	58	Reference	115	Reference	228	Reference
4.92 - 6.83	157	1.104 (0.85,1.44)	49	0.973 (0.62,1.52)	94	0.892 (0.65,1.23)	241	1.064 (0.86,1.32)
6.83 - 9.40	148	1.054 (0.78,1.43)	42	0.913 (0.53,1.57)	91	0.713 (0.49,1.03)	198	0.808 (0.62,1.05)
> 9.40	146	0.981 (0.69,1.40)	40	0.731 (0.37,1.38)	101	0.863 (0.57,1.31)	196	1.012 (0.75,1.37)
Fatty acids (saturated) (g)								
< 13.29	155	Reference	57	Reference	112	Reference	237	Reference
13.29 - 18.03	160	1.145 (0.87,1.50)	48	0.877 (0.55,1.39)	86	0.902 (0.64,1.26)	237	1.035 (0.83,1.29)
18.03 - 24.12	146	1.095 (0.78,1.53)	49	1.466 (0.82,2.61)	104	1.022 (0.69,1.50)	199	0.918 (0.69,1.22)
> 24.12	151	1.345 (0.91,1.98)	35	0.625 (0.30,1.30)	99	1.101 (0.69,1.75)	190	0.922 (0.66,1.29)
Cholesterol (mg)								
< 150.16	175	Reference	56	Reference	94	Reference	236	Reference
150.16 - 208.57	154	0.933 (0.73,1.19)	45	0.813 (0.53,1.25)	105	1.15 (0.84,1.57)	207	0.92 (0.74,1.14)
208.57 - 290.66	130	0.787 (0.59,1.05)	47	1.068 (0.66,1.73)	96	1.052 (0.74,1.50)	192	0.931 (0.73,1.19)
> 290.66	153	1.149 (0.83,1.59)	41	0.622 (0.34,1.13)	106	1.345 (0.90,2.00)	228	1.068 (0.81,1.41)
Micronutrients/vitamins								
Vitamin A (µg)[1]								
< 459.02	171	Reference	58	Reference	111	Reference	258	Reference
459.02 - 669.03	176	1 (0.79,1.27)	48	0.973 (0.64,1.49)	89	0.842 (0.62,1.15)	227	0.931 (0.76,1.14)
669.03- 966.58	134	0.711 (0.53,0.94)	42	0.831 (0.50,1.37)	95	0.879 (0.63,1.23)	189	0.737 (0.58,0.94)
>= 966.58	131	0.72 (0.52,1.01)	41	0.767 (0.43,1.37)	106	0.838 (0.57,1.22)	189	0.687 (0.52,0.91)
Vitamin B1 (thiamin) (mg)								
< 0.85	162	Reference	56	Reference	109	Reference	239	Reference
0.85 - 1.15	161	0.904 (0.70,1.17)	50	0.88 (0.56,1.38)	91	0.849 (0.61,1.18)	226	0.943 (0.76,1.17)
1.15 - 1.56	149	1.058 (0.77,1.45)	33	0.853 (0.47,1.56)	92	0.71 (0.48,1.05)	208	0.908 (0.70,1.18)
>= 1.56	140	0.927 (0.64,1.34)	50	1.143 (0.62,2.11)	109	0.933 (0.61,1.43)	190	0.721 (0.52,1.00)
Vitamin B2 (riboflavin) (mg)								
< 1.31	164	Reference	66	Reference	110	Reference	259	Reference
1.31 - 1.79	153	0.838 (0.65,1.08)	35	0.533 (0.33,0.86)	96	0.967 (0.70,1.33)	219	0.792 (0.64,0.98)
1.79 - 2.45	162	0.957 (0.72,1.28)	42	0.766 (0.46,1.27)	94	0.845 (0.59,1.22)	199	0.735 (0.57,0.94)
>= 2.45	133	0.801 (0.56,1.14)	46	0.869 (0.48,1.56)	101	0.81 (0.53,1.24)	186	0.652 (0.48,0.88)

Table 5 (cont.)

Vitamin B2 (niacin) (mg)								
< 13.96	169	Reference	54	Reference	117	Reference	236	Reference
13.96 - 18.41	147	0.865 (0.66,1.12)	42	0.912 (0.57,1.46)	86	0.763 (0.55,1.06)	236	0.991 (0.80,1.23)
18.41 - 24.39	154	1.004 (0.74,1.36)	49	1.449 (0.85,2.46)	91	0.702 (0.48,1.02)	202	0.927 (0.71,1.21)
>= 24.39	142	0.847 (0.59,1.21)	44	0.882 (0.47,1.67)	107	0.948 (0.63,1.43)	189	0.78 (0.57,1.07)
Vitamin B6 (pyridopsine) (mg)								
< 1.45	176	Reference	57	Reference	110	Reference	247	Reference
1.45 - 1.97	153	0.801 (0.62,1.04)	46	0.789 (0.50,1.24)	90	0.87 (0.63,1.21)	228	0.866 (0.70,1.08)
1.97 - 2.67	145	0.799 (0.59,1.08)	42	0.84 (0.49,1.44)	96	0.69 (0.47,1.01)	203	0.749 (0.58,0.97)
>= 2.67	138	0.735 (0.51,1.05)	44	0.658 (0.34,1.25)	105	0.758 (0.49,1.17)	185	0.636 (0.46,0.88)
Vitamin B12 (cobalamin) (µg)								
< 3.25	161	Reference	52	Reference	118	Reference	257	Reference
3.25 - 4.79	156	0.981 (0.76,1.26)	48	1.148 (0.74,1.78)	89	0.869 (0.64,1.18)	209	0.816 (0.66,1.01)
4.79 - 7.00	164	1.188 (0.90,1.56)	44	1.217 (0.74,2.01)	96	0.764 (0.54,1.07)	195	0.779 (0.61,0.99)
>= 7.00	131	0.894 (0.64,1.24)	45	0.997 (0.57,1.75)	98	0.814 (0.56,1.19)	202	0.804 (0.61,1.05)
Folate (µg)²								
< 321.04	171	Reference	61	Reference	99	Reference	233	Reference
321.04 - 468.89	146	0.821 (0.63,1.06)	46	0.776 (0.50,1.20)	97	1.026 (0.74,1.41)	252	1.103 (0.89,1.36)
468.89 - 674.64	155	0.862 (0.65,1.14)	35	0.666 (0.40,1.11)	101	1.006 (0.71,1.43)	187	0.862 (0.67,1.10)
>= 674.64	140	0.89 (0.65,1.22)	47	0.756 (0.44,1.31)	104	0.948 (0.64,1.41)	191	0.756 (0.57,1.00)
Vitamin C (mg)								
< 59.42	159	Reference	59	Reference	97	Reference	243	Reference
59.42 - 101.11	156	0.985 (0.77,1.26)	48	0.769 (0.51,1.16)	103	0.998 (0.74,1.35)	201	0.803 (0.65,0.99)
101.11 - 154.94	156	0.949 (0.73,1.24)	36	0.735 (0.45,1.19)	76	0.666 (0.47,0.94)	214	0.836 (0.67,1.04)
>= 154.94	141	0.954 (0.69,1.32)	46	0.588 (0.33,1.04)	125	0.924 (0.63,1.35)	205	0.751 (0.57,0.99)
Choline (mg)								
< 218.15	170	Reference	58	Reference	100	Reference	226	Reference
218.15 - 293.19	154	0.942 (0.72,1.22)	47	0.781 (0.50,1.22)	91	0.936 (0.67,1.31)	224	1.002 (0.80,1.25)
293.19 - 394.23	146	0.815 (0.59,1.12)	42	0.913 (0.52,1.60)	101	0.919 (0.62,1.36)	212	1.012 (0.77,1.33)
>= 395.23	142	1.095 (0.74,1.62)	42	0.569 (0.28,1.15)	109	0.954 (0.60,1.51)	201	0.854 (0.61,1.20)

Table 5 (cont.)

Vitamin E (mg)								
< 3.43	169	Reference	57	Reference	174	Reference	251	Reference
3.43 - 4.91	160	0.823 (0.64,1.06)	50	0.711 (0.45,1.12)	139	0.86 (0.62,1.19)	206	0.984 (0.79,1.22)
4.91 - 7.16	150	0.967 (0.72,1.31)	41	0.876 (0.53,1.44)	160	0.788 (0.54,1.15)	203	0.789 (0.60,1.03)
>= 7.16	133	0.748 (0.53,1.05)	41	0.367 (0.19,0.70)	157	0.763 (0.51,1.15)	203	0.673 (0.50,0.91)
Beta-carotene (µg)								
< 1165.30	171	Reference	58	Reference	101	Reference	241	Reference
1165.30 - 2170.75	176	0.89 (0.70,1.13)	48	0.713 (0.47,1.08)	85	0.867 (0.63,1.18)	205	0.882 (0.72,1.08)
2170.75 - 3770.20	134	0.852 (0.65,1.11)	42	0.707 (0.45,1.11)	108	1.093 (0.80,1.49)	212	0.895 (0.72,1.11)
>= 3770.20	131	0.861 (0.64,1.15)	41	0.711 (0.43,1.18)	107	0.918 (0.65,1.30)	205	0.782 (0.61,1.00)
Methionine								
< 1.07	176	Reference	52	Reference	116	Reference	245	Reference
1.07 - 1.41	144	0.795 (0.61,1.03)	47	0.95 (0.61,1.49)	80	0.697 (0.50,0.97)	212	0.869 (0.70,1.08)
1.41 - 1.85	142	0.825 (0.61,1.12)	47	1.367 (0.79,2.37)	99	0.866 (0.60,1.24)	196	0.842 (0.65,1.09)
>= 1.85	150	0.905 (0.63,1.29)	43	1.159 (0.58,2.35)	106	0.904 (0.59,1.39)	210	0.935 (0.68,1.28)
Elements								
Iron (mg)								
< 8.37	180	Reference	53	Reference	112	Reference	246	Reference
8.37 - 12.32	139	0.763 (0.59,0.99)	43	0.864 (0.54,1.39)	92	0.836 (0.61,1.15)	206	0.795 (0.64,0.99)
12.32 - 17.46	162	0.988 (0.75,1.30)	39	1.229 (0.74,2.05)	104	0.754 (0.53,1.07)	236	1.029 (0.81,1.30)
>= 17.46	131	0.742 (0.53,1.04)	54	1.173 (0.68,2.03)	93	0.693 (0.46,1.05)	175	0.583 (0.43,0.79)
Zinc (mg)								
< 7.77	163	Reference	49	Reference	112	Reference	251	Reference
7.77 - 10.40	144	0.91 (0.69,1.20)	49	1.191 (0.73,1.93)	74	0.765 (0.53,1.10)	217	0.831 (0.66,1.04)
10.40 - 13.80	164	1.105 (0.80,1.53)	52	2.139 (1.21,3.78)	108	1.136 (0.77,1.68)	210	0.807 (0.61,1.07)
>= 13.80	141	0.914 (0.63,1.32)	39	0.683 (0.34,1.39)	107	0.915 (0.59,1.41)	185	0.684 (0.49,0.95)
Copper (mg)								
< 0.69	178	Reference	57	Reference	96	Reference	221	Reference
0.69 - 0.94	149	0.797 (0.60,1.05)	41	0.754 (0.46,1.23)	95	0.956 (0.67,1.36)	222	0.97 (0.76,1.23)
0.94 -1.32	158	0.97 (0.69,1.37)	49	0.957 (0.53,1.72)	96	1.17 (0.75,1.82)	237	1.106 (0.82,1.48)
>= 1.32	127	0.702 (0.46,1.07)	42	0.472 (0.23,0.99)	114	0.974 (0.61,1.56)	183	0.615 (0.42,0.89)

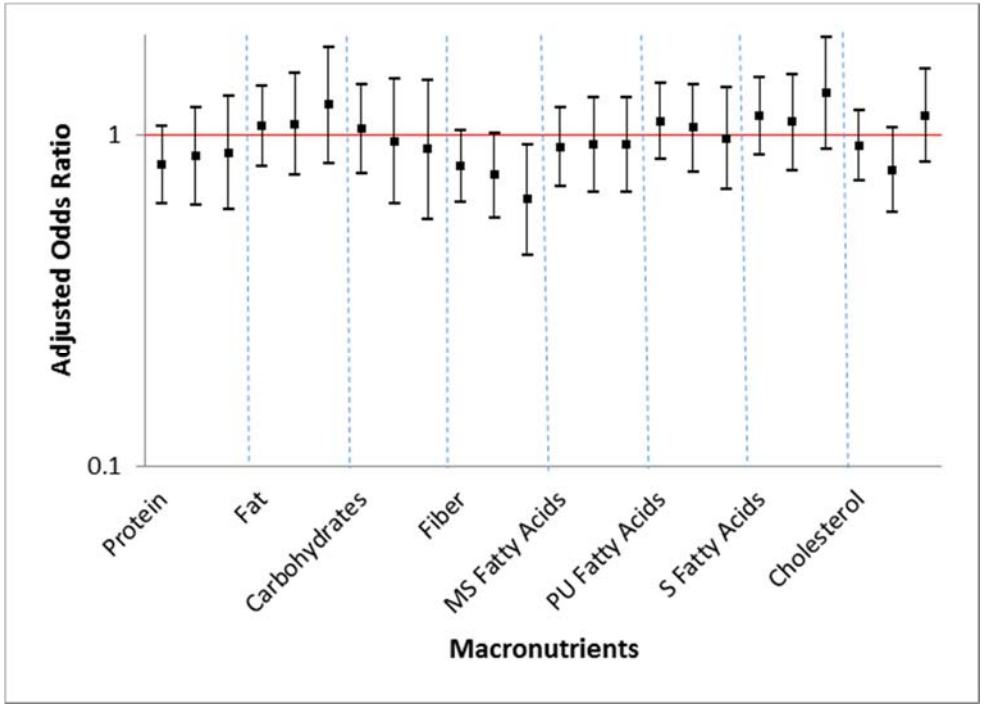
Table 5 (cont.)

Calcium (mg)								
< 521.80	162	Reference	50	Reference	111	Reference	255	Reference
521.80 - 760.96	163	0.95 (0.74,1.22)	56	1.273 (0.82,1.97)	104	0.982 (0.72,1.34)	245	0.964 (0.78,1.19)
760.96 - 1077.80	143	0.78 (0.58,1.05)	42	1.143 (0.67,1.95)	83	0.661 (0.46,0.96)	185	0.76 (0.59,0.98)
>= 1077.80	144	0.848 (0.60,1.19)	41	0.901 (0.48,1.67)	103	1.019 (0.67,1.54)	178	0.74 (0.55,1.00)
Magnesium (mg)								
< 175.78	175	Reference	53	Reference	102	Reference	240	Reference
175.78 - 232.63	158	0.808 (0.62,1.05)	49	1.07 (0.66,1.73)	96	0.96 (0.68,1.35)	221	0.865 (0.69,1.09)
232.63 - 311.99	138	0.664 (0.47,0.94)	48	1.145 (0.64,2.05)	94	0.868 (0.57,1.32)	223	0.882 (0.66,1.17)
>= 311.99	140	0.696 (0.46,1.05)	39	0.419 (0.19,0.91)	109	0.791 (0.48,1.29)	179	0.514 (0.35,0.75)
Selenium (µg)								
< 57.88	164	Reference	50	Reference	104	Reference	225	Reference
57.88 - 75.91	145	0.894 (0.68,1.17)	51	1.322 (0.83,2.11)	94	0.826 (0.59,1.15)	221	1.038 (0.83,1.30)
75.91 - 99.56	160	1.166 (0.84,1.62)	46	1.333 (0.74,2.39)	90	1.077 (0.71,1.63)	221	1.069 (0.81,1.41)
>= 99.56	143	0.935 (0.64,1.37)	42	0.745 (0.36,1.54)	113	1.08 (0.69,1.69)	196	0.853 (0.61,1.20)

* Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center; [1] Vitamin A as retinol activity equivalent; [2] Folate as dietary folate equivalent

Figure 4.

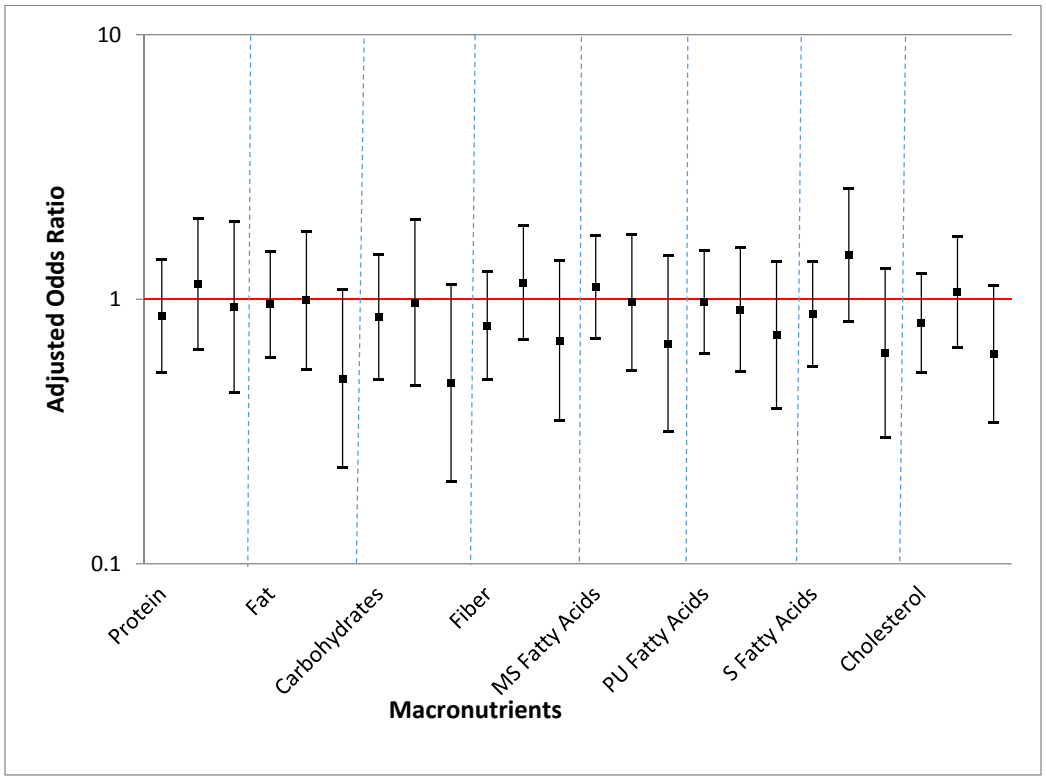
A. *Adjusted* odds ratios[1] of esophageal atresia/stenosis risk by quartile of self-reported macronutrient intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits

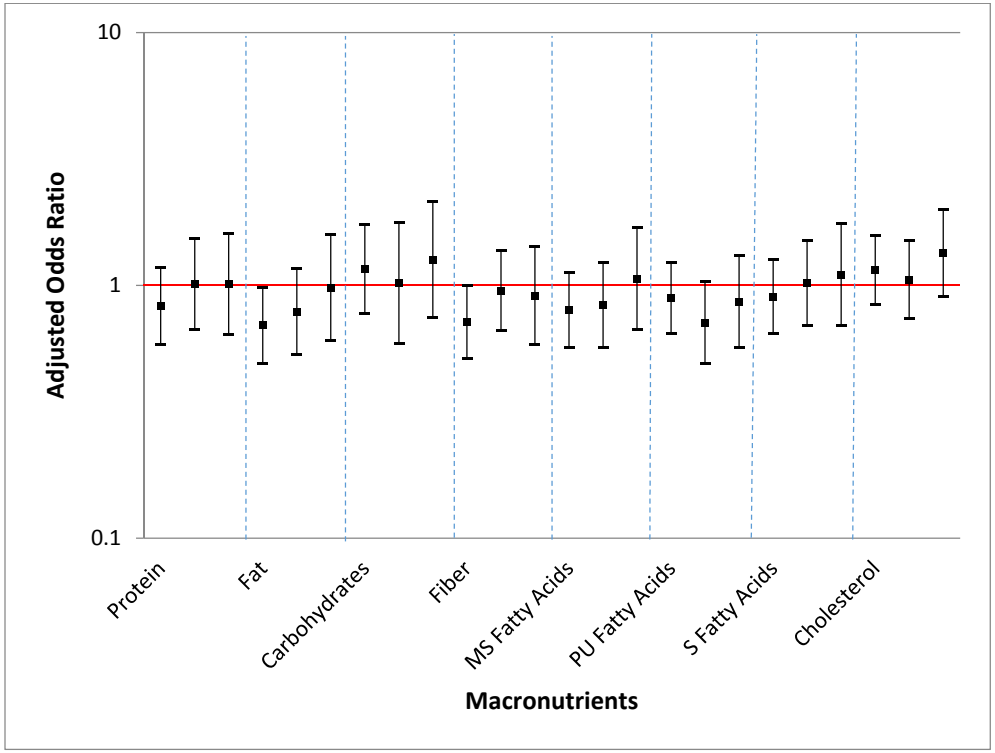
B. *Adjusted* odds ratios[1] of duodenal atresia/stenosis risk by quartile of self-reported macronutrient intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits

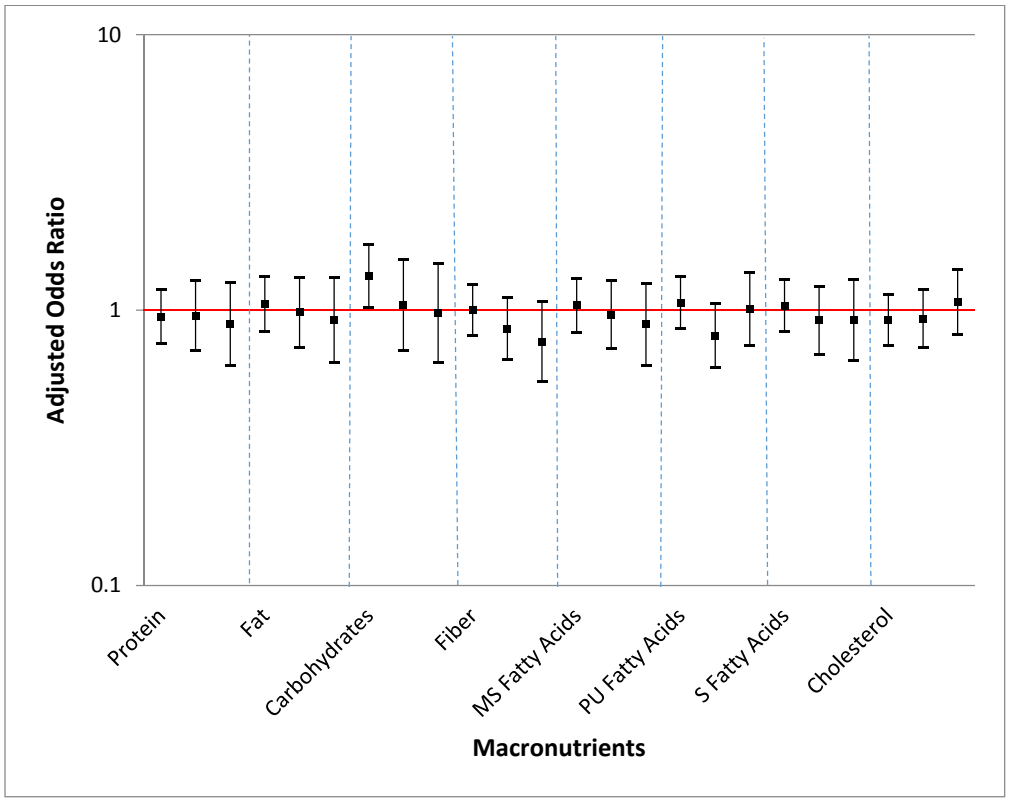
C. *Adjusted* odds ratios[1] of jejunal/ileal atresia/stenosis risk by quartile of self-reported macronutrient intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits

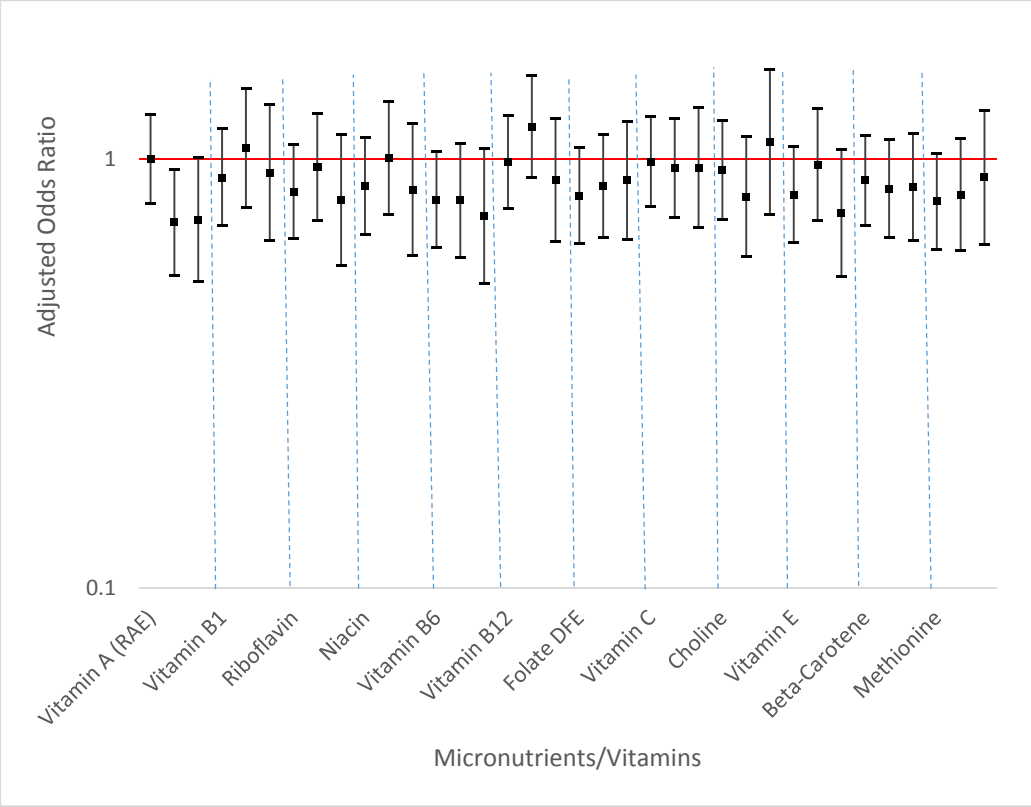
D. *Adjusted* odds ratios[1] of anorectal atresia/stenosis risk by quartile of self-reported macronutrient intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits

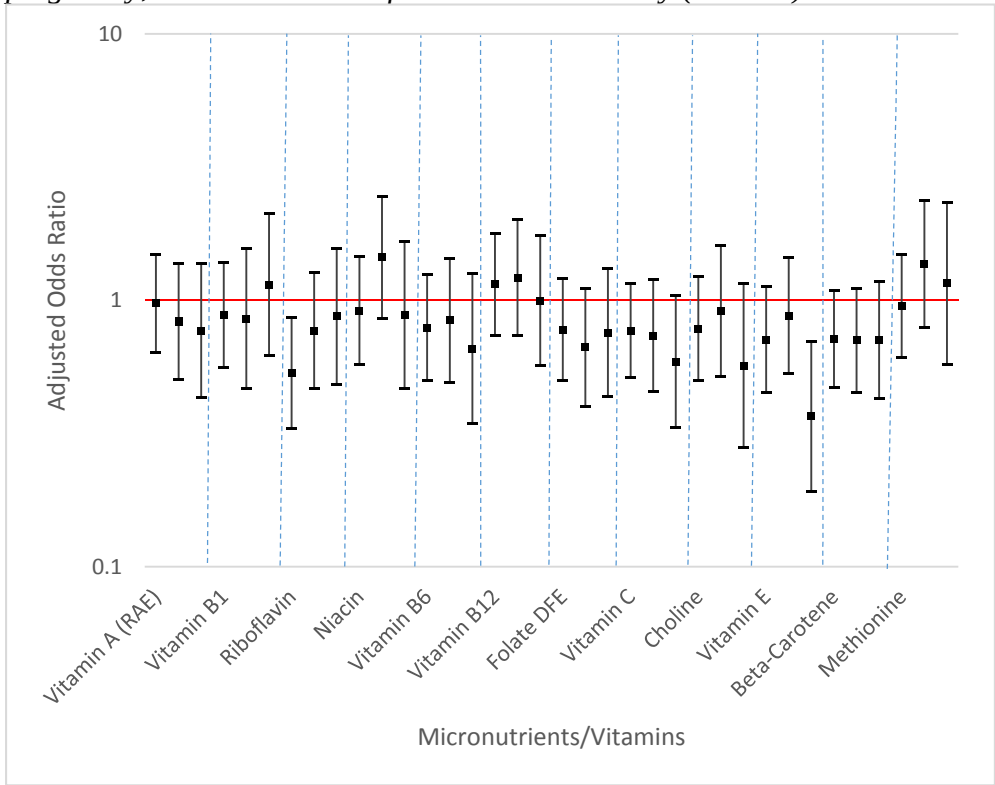
E. *Adjusted* odds ratios[1] of esophageal atresia/stenosis risk by quartile of self-reported micronutrient/vitamin[2] intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits; [2] Vitamin A as retinol activity equivalent, folate as dietary folate equivalent

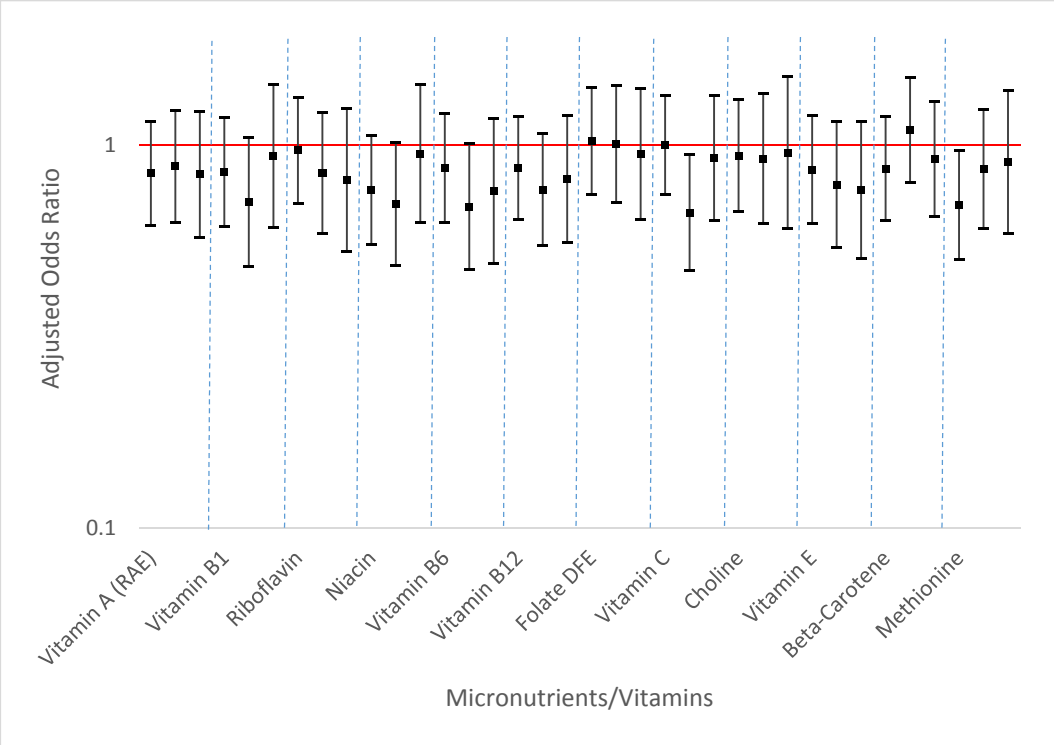
F. *Adjusted* odds ratios[1] of duodenal atresia/stenosis risk by quartile of self-reported micronutrient/vitamin[2] intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits; [2] Vitamin A as retinol activity equivalent, folate as dietary folate equivalent

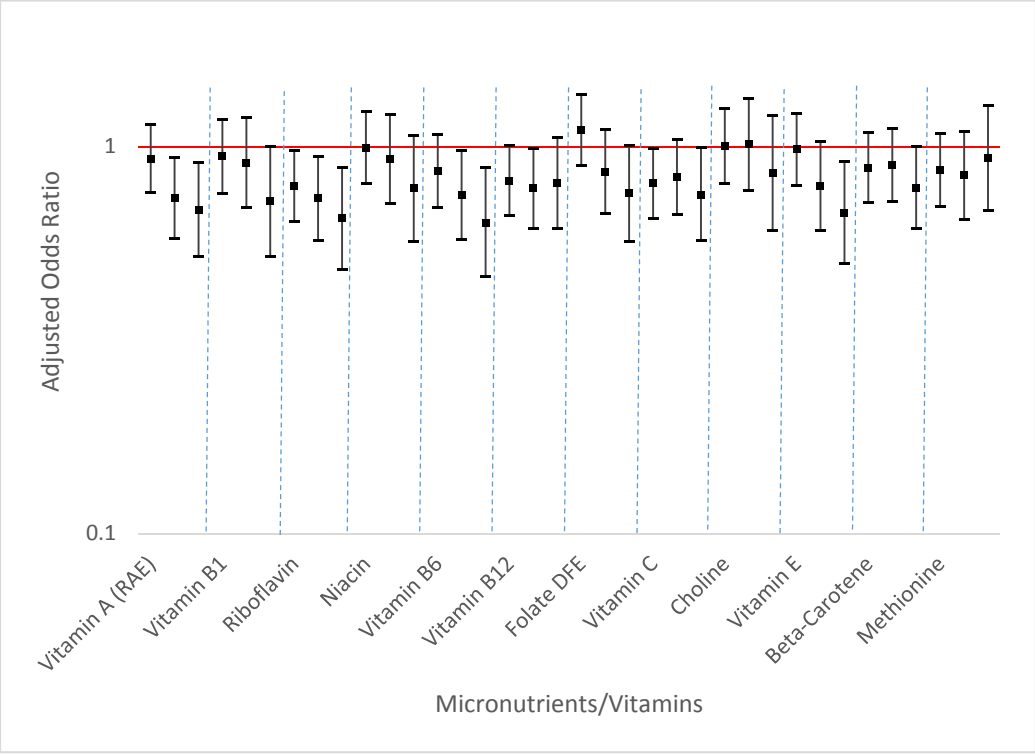
G. *Adjusted* odds ratios[1] of jejunal/ileal atresia/stenosis risk by quartile of self-reported micronutrient/vitamin[2] intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits; [2] Vitamin A as retinol activity equivalent, folate as dietary folate equivalent

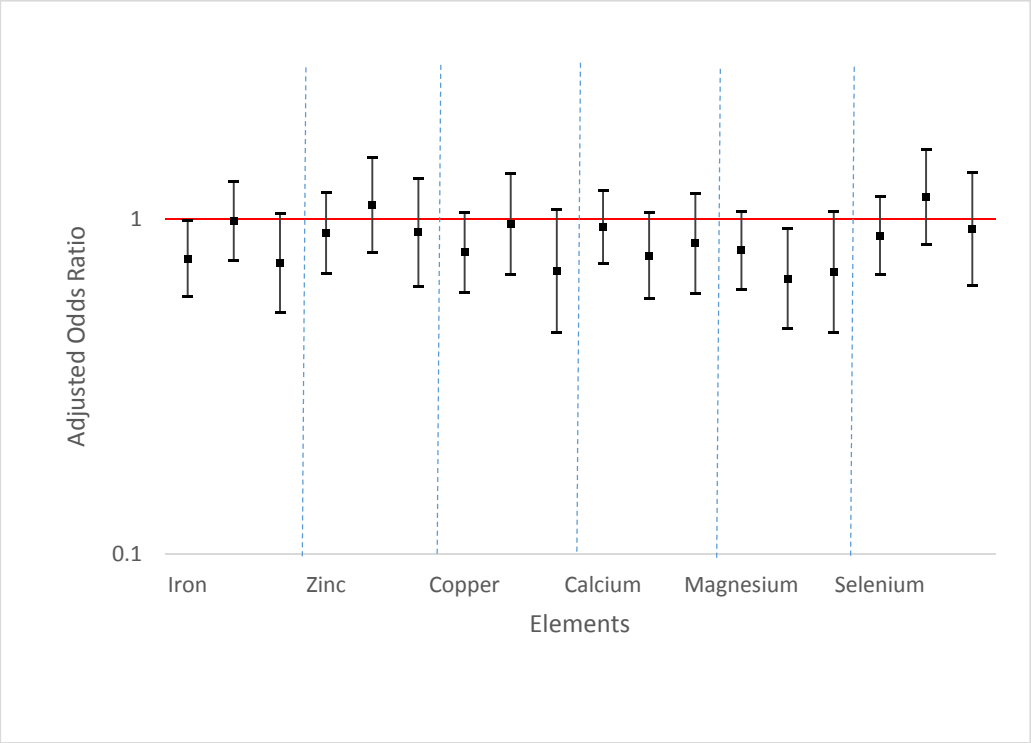
H. *Adjusted* odds ratios[1] of anorectal atresia/stenosis risk by quartile of self-reported micronutrient/vitamin[2] intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits; [2] Vitamin A as retinol activity equivalent, folate as dietary folate equivalent

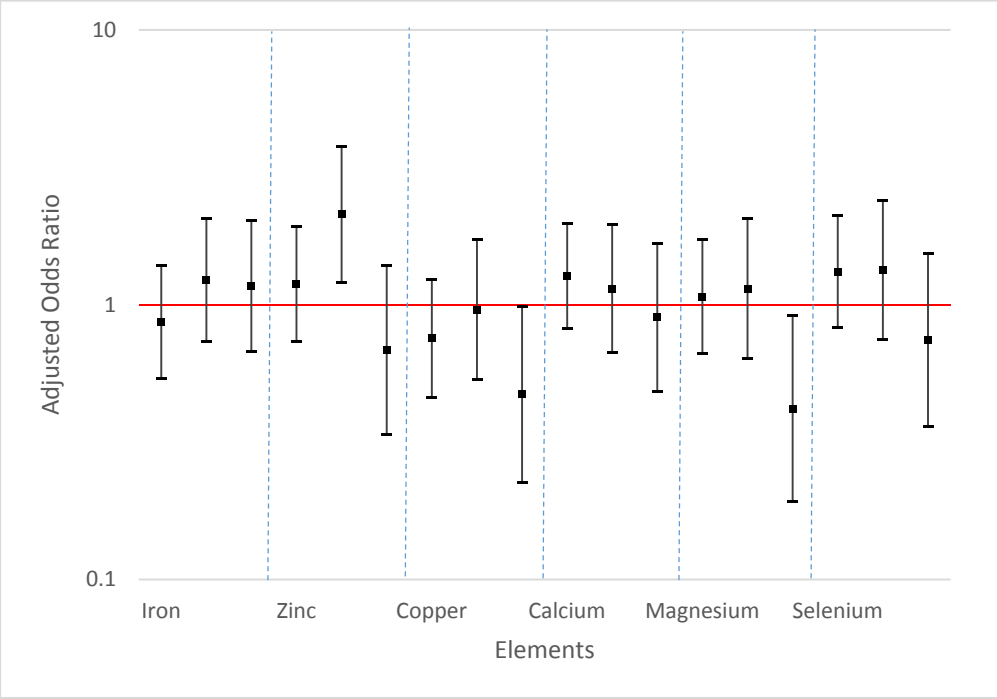
I. *Adjusted* odds ratios[1] of esophageal atresia/stenosis risk by quartile of self-reported element intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits

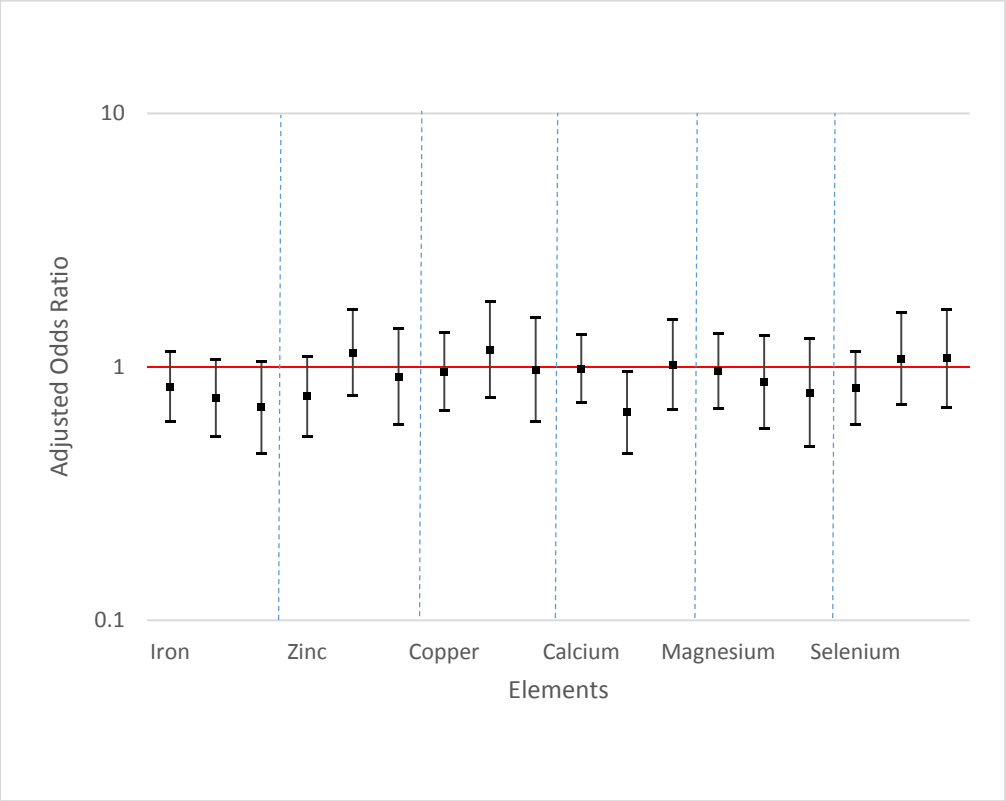
J. *Adjusted* odds ratios[1] of duodenal atresia/stenosis risk by quartile of self-reported element intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits

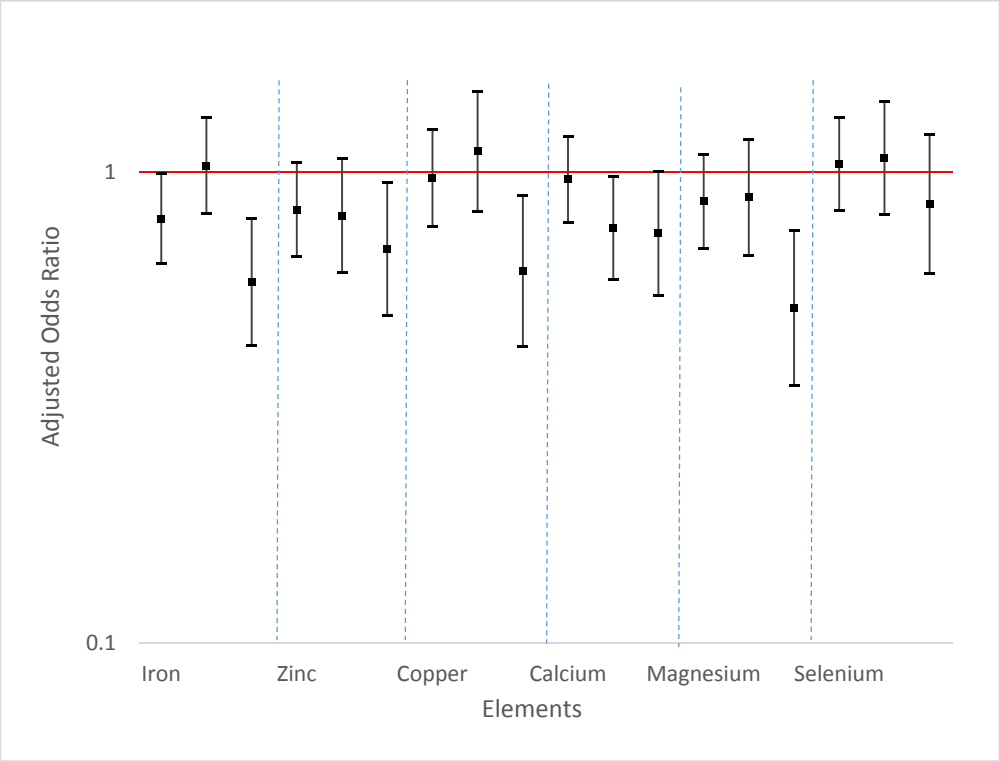
K. *Adjusted* odds ratios[1] of jejunal/ileal atresia/stenosis risk by quartile of self-reported element intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits

L. *Adjusted* odds ratios[1] of anorectal atresia/stenosis risk by quartile of self-reported element intake in the year before pregnancy, National Birth Defects Prevention Study (NBPDS) 1997-2009*



***** Odds ratios adjusted for maternal age, race/ethnicity, education level, BMI, number of previous pregnancies, first trimester nausea and/or vomiting, use of folate supplements, total energy intake, and study center

[1] Odds ratios represent odds of atresia/stenosis for 2nd through 4th quartile of nutrient intake compared to odds of atresia/stenosis for 1st quartile of intake, respectively; bands represent 95% Wald confidence limits

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